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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/835,287	04/13/2001	David R. Kaplan	071957-1102	4744

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Michael A. Whittaker
FOLEY & LARDNER
23rd Floor
402 West Broadway
San Diego, CA 92101-3542

EXAMINER
GABEL, GAILENE

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/835,287	KAPLAN, DAVID R.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *21-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-36* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election, without traverse, of Group 1, claims 1-20, filed 8/13/02 in Paper No. 8 is acknowledged. Claims 21-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention. Currently, claims 1-36 are pending. Claims 1-20 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 step b) has improper antecedent basis problem in reciting, "in cells". Change to "in the cells" for proper antecedent basis.

Claim 1 is incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Specifically, there is no correlation step that correlates the detected signal in step d) with the presence of intracellular analyte as required by the preamble.

Claim 2 step b) has improper antecedent basis problem in reciting, "in cells". Change to "in the cells" for proper antecedent basis.

Claim 2 is incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Specifically, there is no correlation step that correlates the detected signal in step d) with the presence of intracellular analyte as required by the preamble.

Claims 3-20 have improper antecedent basis problems in reciting, "A method according to claim ...".

Claim 5 step i) fails to recite a positive limitation in the claim is indefinite in reciting, "capable of".

Claim 5 step iii) has improper antecedent basis problem in reciting, "in cells". Change to "in the cells" for proper antecedent basis.

Claim 10 step i) fails to recite a positive limitation in the claim is indefinite in reciting, "capable of".

Claim 15 is indefinite in reciting overlapping Markush groups in a Markush claim. Further, it is unclear how "cytoplasmic antigens" and "cytoskeletal molecules" are intracellular antigens since they appear to be cell surface antigens.

Claim 20 is vague and indefinite in reciting, "A kit for performing a method according to claim 1 or 2." because it fails to define what limitations, i.e. elements of a kit, are included or excluded in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-13 and 15-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Karkmann et al. (Journal of Immunological Methods, 1999) in view of Roth et al. (US 5,902,727).

Karkmann et al. teach a method of detecting intracellular analyte, i.e. cytokines in tumor cells, in cells by flow cytometry using intracellular tyramine-based signal amplification technique (see Abstract and page 114, column 1). Karkmann et al. teach fixing peripheral blood mononuclear cells (PBMC) with formaldehyde, pemeabilizing the cells with 0.5% saponin, and resuspending the cells in a buffer medium containing bovine serum albumin (BSA) and 0.5% saponin (see page 114, column 2 to page 115, column 1). Thereafter, Karkmann et al. teach staining the cells with fluorescein-labeled antibodies against the intracellular analyte which is linked to horseradish-peroxidase directly or indirectly by biotinylation, i.e. avidin-biotin, then adding tyramide substrate, wherein the peroxidase enzyme catalyzes the deposition of the tyramide in the cells comprising intracellular analyte. After the step of staining the cells with labeled antibodies, the cells are washed twice with saponin buffer to remove unbound binding partners (see page 115, column 2). Karkmann et al. specifically taught that while saponin is usually used as a permeabilization agent for intracellular staining, it is also capable of blocking peroxidase activity; thus, reducing nonspecific background staining or contamination staining. According to Karkmann et al., the tyramine-based signal amplification technique results in a 10 to 15 fold improvement of the signal compared to

standard flow cytometric techniques using fluorescent label making it possible to detect even weakly stained cells (see page 116, column 2, pages 117 and 119).

Karkmann et al. differ from the instant invention in failing to disclose washing the cells in a medium comprising chaotropic agent after deposition of tyramide in the cells.

Roth et al. disclose that sensitivity of detection by labeled antibodies is increased by standard amplification methods such as tyramide signal amplification methods. Roth et al. specifically disclose that quantitation aspects of tyramide signal amplification methods rely upon solution phase generation of enzyme reaction product which proceed to end point; or alternatively, can be terminated by removal of the solution phase from the enzyme or addition of denaturing agents (reducing agents) such as chaotropic agents, acids, and bases. See columns 7-8.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have incorporated the chaotropic agent as taught by Roth, into the tyramide signal amplification method of detecting intracellular analyte as taught by Karkmann, because Roth specifically taught that solution phase generation of enzyme product in tyramide signal amplification methods can be removed using chaotropic agents; thus, providing motivation to increase sensitivity in the quantitation aspect of tyramide signal amplification in the method of Karkmann.

Karkmann et al. and Roth et al. differ from the instant invention in failing to teach a signal provided by the method that is at least 20-fold and 50-fold greater than a signal by standard flow cytometry methods, as recited in claims 3-4.

However, the discovery of a degree of amplification signal of a known method, i.e. at least 20-fold and 50-fold greater than a signal by standard flow cytometry methods, are all result effective variables which the prior art references have shown may be obtained by optimization procedures. It has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "No invention is involved in discovering optimum ranges of a process by routine experimentation." Id. at 458, 105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272, 276, 205 USPQ 215, 218-219 (C.C.P.A. 1980). Since Applicant has not disclosed that the specific limitations recited in instant claims 3-4 are for any particular purpose or solve any stated problem and the prior art teaches that tyramide amplification methods often vary according to various matrices used and parameters appear to work equally as well, absent unexpected results, it would have been obvious for one of ordinary skill to discover the optimum workable ranges of the methods disclosed by the prior art by normal optimization procedures.

4. Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lollini et al. (Immunological Blackboard, 1998) in view of Roth et al. (US 5,902,727).

Lollini et al. teach a method and kit for detecting intracellular analyte, i.e. oncosuppressor protein p53, in osteosarcoma cells wherein flow cytometric detection is performed after tyramide signal amplification (see Abstract). Lollini et al. teach culturing

the cells in fetal bovine albumin (FBS), harvesting the cells, fixing the cells with methanol, and completely pemeabilizing the cells with methanol or acetone. Thereafter, Lollini et al. resuspend the cells with analyte specific antibody, i.e. anti-p53, in a buffer medium containing PBS, BSA and TWEEN 20. After the step of staining the cells with labeled antibodies, the cells are further washed further with a medium containing PBS, BSA and TWEEN 20, to remove unbound binding partners from the suspension. In practice, Lollini et al. teach incorporating a primary antibody against the intracellular analyte into the cells, and then adding thereto a horseradish peroxidase-conjugated $F(ab')_2$ anti-mouse IgG. Thereafter, the cells are resuspended in fluorescein tyramide substrate so that the peroxidase enzyme catalyzes the deposition of tyramide in the cells (see pages 1-2). According to Lollini et al., the tyramide signal amplification is an excellent system for the quantitative determination of intracellular antigens in cells by flow cytometry and is superior to standard flow cytometric assays, because of its capability to yield 10 to 15 stronger signal (see page 5).

Lollini et al. differ from the instant invention in failing to disclose washing the cells in a medium comprising chaotropic agent after deposition of tyramide in the cells.

Roth et al. has been discussed supra.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have incorporated the chaotropic agent as taught by Roth, into the tyramide signal amplification method of detecting intracellular analyte as taught by Lollini, because Roth specifically taught that solution phase generation of enzyme product in tyramide signal amplification methods can be removed using chaotropic

agents; thus, providing motivation to increase sensitivity in the quantitation aspect of tyramide signal amplification in the method of Lollini.

Lollini et al. and Roth et al. differ from the instant invention in failing to teach a signal provided by the method that is at least 20-fold and 50-fold greater than a signal by standard flow cytometry methods, as recited in claims 3-4.

However, the discovery of a degree of amplification signal of a known method, i.e. at least 20-fold and 50-fold greater than a signal by standard flow cytometry methods, are all result effective variables which the prior art references have shown may be obtained by optimization procedures. It has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "No invention is involved in discovering optimum ranges of a process by routine experimentation." Id. at 458, 105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272, 276, 205 USPQ 215, 218-219 (C.C.P.A. 1980). Since Applicant has not disclosed that the specific limitations recited in instant claims 3-4 are for any particular purpose or solve any stated problem and the prior art teaches that tyramide amplification methods often vary according to various matrices used and parameters appear to work equally as well, absent unexpected results, it would have been obvious for one of ordinary skill to discover the optimum workable ranges of the methods disclosed by the prior art by normal optimization procedures.

5. No claims are allowed.

Remarks

6. Prior art made of record are not relied upon but considered pertinent to the applicants' disclosure:

Chao et al. (Cytometry, 1996) compares immunofluorescence signal between cell surface antigen application and intracellular analyte staining in amplification methods by enzyme catalyzed deposition of tyramide (fluorescent reporter substrate) (see specifically the Abstract and page 50-51).

McIntyre et al. (Journal of Immunological Methods, 1994) teach quantitation of intracytoplasmic cytokines using two-color, immunofluorescent flow cytometry.

Hopman et al. (The Journal of Histochemistry and Cytochemistry, 1998) teach preparation of various tyramide conjugates for use in CARD amplification.

LI et al. (Proceedings of the American Association for Cancer Research Annual Meeting, March 2000) teach measuring DNA adduct by dual fluorescence labeling, laser scanning cytometry, and tyramide signal amplification.

Moritoyo et al. (Journal of Neurovirology, June 1999) teach detecting HTLV-I p40 protein in a method of immunohistochemistry combined with tyramide signal amplification.

Bobrow et al. (US 5,196,306) disclose a method to catalyze reporter deposition to improve detection of analyte.

Connelly et al. (US 5,442,277) discloses a cell fixative composition for use in staining cells without destroying the cell surface. The composition includes a fixative and a permeabilizer, i.e. dimethylsulfoxide, in the compositions.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday-Thursday 6:00 AM to 3:30 PM and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (703) 305-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gailene R. Gabel
October 23, 2002

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641